

Amendments to the Specification:

On page 1 of the specification, please insert the following paragraph after the title of the Application:

Please replace the paragraph at page 3, from line 3 through line 14, with the following paragraph:

- --For example, isoformic myosin heavy chain genes are known to be generally expressed in cardiac muscle tissue. In the rodent, the $\{\beta$ MyHC gene is only highly expressed in the fetus and in diseased states such as overt cardiac hypertrophy, heart failure and diabetes; the $\{\alpha$ MyHC gene is highly expressed shortly after birth and continues to be expressed in the adult heart. In the human, however, $\{\beta$ MyHC is highly expressed in the ventricles from the fetal stage through adulthood. This highly expressed $\{\beta$ MyHC, which harbours several mutations, has been demonstrated to be involved in familial hypertrophic cardiomyopathy (Geisterfer-Lowrance *et al.* 1990). It was reported that mutations of $\{\beta$ MyHC can be detected by PCR using blood lymphocyte DNA (Ferrie *et al.*, 1992). Most recently, it was also demonstrated that mutations of the myosin-binding protein C in familial hypertrophic cardiomyopathy can be detected in the DNA extracted from lymphocytes (Niimura *et al.*, 1998).--

Please replace the paragraph at page 7, from line 3 through line 14, with the following paragraph:

--Figure 1 shows the following RNA samples prepared from human blood; Figure 1A: Lane 1, Molecular weight marker; Lane 2, RT-PCR on APP gene; Lane 3, PCR on APP gene; Lane 4, RT-PCR on APC gene; Lane 5, PCR on APC gene; Figure 1B: Lanes 1 and 2, RT-PCR and PCR of $\{\beta$ MyHC, respectively; Lanes 3 and 4, RT-PCR of $\{\beta$ MyHC from RNA prepared from human fetal and human adult heart, respectively; Lane 5, Molecular weight marker.--

Please replace the paragraph at page 12, from line 22 through page 13, line 16, with the following paragraph:

--A standard Northern blot assay can be used to ascertain the relative amounts of mRNA in a cell or tissue obtained from plant or other tissue, in accordance with conventional Northern hybridization techniques known to those persons of ordinary skill in the art. The Northern blot uses a hybridization probe, e.g. radiolabelled cDNA, either containing the full-length, single stranded DNA or a fragment of that DNA sequence at least 20 (preferably at least 30, more preferably at least 50, and most preferably at least 100 consecutive nucleotides in length). The DNA hybridization probe can be labelled by any of the many different methods known to those skilled in this art. The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals which fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be utilized as labels. These include, for example, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate. Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. The preferred isotope may be selected from ^3H , ^{14}C , ^{32}P , ^{35}S , ^{36}Cl , ^{51}Cr , ^{57}Co , ^{58}Co , ^{59}Fe , ^{90}Y , ^{125}I , ^{131}I , and ^{186}Re . Enzyme labels are likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging molecules such as carbodiimides, diisocyanates, glutaraldehyde and the like. Many enzymes which can be used in these procedures are known and can be utilized. The preferred are peroxidase, (β -glucuronidase, (β -D-glucosidase, (β -D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phosphatase. U.S. Patent Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.--

Please replace the paragraph at page 17, from line 22 through line 30, with the following paragraph:

--Nucleic acids (RNA, DNA, cDNA, PCR products or ESTs) ($\sim 40 \mu\text{l}$) are precipitated with $4 \mu\text{l}$ (1/10 volume) of 3M sodium acetate (pH 5.2) and $100 \mu\text{l}$ (2.5 volumes) of ethanol and stored overnight at -20°C . They are then centrifuged at 3,300 rpm at 4°C for 1 hour. The obtained pellets were washed with $50 \mu\text{l}$ ice-cold 70% ethanol and centrifuged again for 30

minutes. The pellets are then air-dried and resuspended well in 50% dimethylsulfoxide (DMSO) or 20 μ l 3X SSC overnight. The samples are then deposited either singly or in duplicate onto Gamma Amino Propyl Silane (Corning CMT-GAPS or CMT-GAP2, Catalog No. 40003, 40004) or polylysine-coated slides (Sigma Cat. No. P0425) using a robotic GMS 417 or 427 arrayer (Affymetrix, CA). The boundaries of the DNA spots on the microarray are marked with a diamond scribe. The invention provides for arrays where 10-20,000 different DNAs are spotted onto a solid support to prepare an array, and also may include duplicate or triplicate DNAs.--

Please replace the paragraph at page 18, from line 1 through line 15, with the following paragraph:

--The arrays are rehydrated by suspending the slides over a dish of warm particle free ddH₂O for approximately one minute (the spots will swell slightly but not run into each other) and snap-dried on a 70-80°C inverted heating block for 3 seconds. DNA is then UV crosslinked to the slide (Stratagene, Stratalinker, 65 mJ – set display to “650” which is 650 x 100 μ J) or baked at 80°C for two to four hours. The arrays are placed in a slide rack. An empty slide chamber is prepared and filled with the following solution: 3.0 grams of succinic anhydride (Aldrich) is dissolved in 189 ml of 1-methyl-2-pyrrolidinone (rapid addition of reagent is crucial); immediately after the last flake of succinic anhydride dissolved, 21.0 ml of 0.2 M sodium borate is mixed in and the solution is poured into the slide chamber. The slide rack is plunged rapidly and evenly in the slide chamber and vigorously shaken up and down for a few seconds, making sure the slides never leave the solution, and then mixed on an orbital shaker for 15-20 minutes. The slide rack is then gently plunged in 95°C ddH₂O for 2 minutes, followed by plunging five times in 95% ethanol. The slides are then air dried by allowing excess ethanol to drip onto paper towels. The arrays are then stored in the slide box at room temperature until use.--

Please replace the paragraph at page 23, from line 3 through line 11, with the following paragraph:

--2 μ g Oligo-dT primers are annealed to 2 μ g of mRNA isolated from a blood sample of a patient in a total volume of 15 μ l, by heating to 70°C for 10 min, and cooled on ice. The

mRNA is reverse transcribed by incubating the sample at 42°C for 1.5-2 hours in a 100 µl volume containing a final concentration of 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM MgCl₂, 25 mM DTT, 25 mM unlabeled dNTPs, 400 units of Superscript II (200 U/µl, Gibco BRL), and 15 mM of Cy3 or Cy5 (Amersham). RNA is then degraded by addition of 15µl of 0.1N NaOH, and incubation at 70°C for 10 min. The reaction mixture is neutralized by addition of 15µl of 0.1N HCL, and the volume is brought to 500µl with TE (10mM Tris, 1mM EDTA), and 20 µg of Cot1 human DNA (Gibco-BRL) is added.--

Please replace the paragraph at page 34, from line 13 through line 18, with the following paragraph:

--RNA extracted from samples of human tissue was used for RT-PCR analysis (Jin *et al.* 1990). Three pairs of forward and reverse primers were designed for human cardiac beta-myosin heavy chain gene (β MyHC), amyloid precursor protein (APP) gene and adenomatous polyposis-coli protein (APC) gene. The PCR products were also subjected to automated DNA sequencing to verify the sequences as derived from the specific transcripts of blood.--

Please replace the paragraph at page 34, from line 22 through line 26, with the following paragraph:

--The beta-myosin heavy chain gene (β MyHC) transcript (mRNA) is known to be highly expressed in ventricles of the human heart. This sarcomeric protein is important for heart muscle contraction and its presence would not be expected in other non-muscle tissues and blood. In 1990, the gene for human cardiac β MyHC was completely sequenced (Liew *et al.* 1990) and was comprised of 41 exons and 42 introns.--

Please replace the paragraph at page 34, from line 27 through page 35, line 3, with the following paragraph:

--The method of reverse transcription polymerase chain reaction (RT-PCR) was used to determine whether this cardiac specific mRNA is also present in human blood. A pair of primers was designed; the forward primer (SEQ ID No. 3) was on the boundary of exons 21 and 22, and the reverse primer (SEQ ID No. 4) was on the boundary of exons 24 and 25. This

region of mRNA is only present in β MyHC and is not found in the alpha-myosin heavy chain gene (α MyHC).--

Please replace the paragraph at page 35, from line 4 through line 8, with the following paragraph:

--A blood sample was first treated with lysing buffer and then undergone centrifuge. The resulting pellets were further processed with RT-PCR. RT-PCR was performed using the total blood cell RNA as a template. A nested PCR product was generated and used for sequencing. The sequencing results were subjected to BLAST and the identity of exons 21 to 25 was confirmed to be from β MyHC (Figure 1A).--